REMARKS

In the Final Office Action dated October 4, 2007, Claims 1-7, 9-15 and 17-20 are pending. The Examiner has made the restriction requirement final. Claims 6 and 12 are withdrawn from consideration as directed to nonelected subject matter. The Examiner alleges that certain figures and tables that were submitted with the previous response lacked labels. Claims 14-15, 17-19 and 20 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support. The Examiner maintains the rejection of Claim 15 under 35 U.S.C. §102(e) as allegedly anticipated by Falsen et al. *(Journal of Systematic Bacteriology* 217-221, 1999). Claims 3 and 20 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. Claim 20 is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement.

This Response addresses each of the Examiner's objections and rejections. Applicants therefore respectfully submit that the present application is in condition for allowance or at least in a better position for appeal. Favorable consideration of all pending claims is therefore respectfully requested.

The Examiner contends that Applicants' submission of Figures 3, 4, 8, 3.7 (Table 4 and 5) together with the previous response was not labeled as exhibits. Therefore, the Examiner has considered Figures 3, 4, 8, 3.7 (Table 4 and 5) as lacking a label. Applicants respectfully submit that in the previously response, Figures 3, 4, and 8 were submitted as Exhibit A, B and C, respectively; Tables 4 and 5 are submitted as Exhibit D. Therefore, Figures 3, 4, 8, Table 4 and 5 are clearly submitted and labeled as exhibits. Applicants request the Examiner to acknowledge previously filed Exhibits A-D and confirm that Figures 3, 4, 8, as well as Table 4 and 5 are properly labeled.

In the Final Action, the Examiner alleges that the population of urogenital microbiota includes bacteria which have structures and properties that are different and distinct from those of the population of intestinal microbiota. The Examiner alleges that the two populations do not necessarily overlap. Therefore, the Examiner has made the restriction requirement final.[1] As a result, Claims 6 and 12 are withdrawn from consideration as directed to nonelected subject matter. The Examiner requires the cancellation of Claims 6 and 12 in response to the Final Action. In this regard, Applicants observe that the Examiner in Item 2 of the Final Action states that Claims 6 and 12 are withdrawn from consideration. However, the Examiner in the end of Item 3 inconsistently states that Claims 1-7, 9-15 and 17-20 are examined. Applicants respectfully request the Examiner's clarification regarding the status of Claims 6 and 12.

Claims 14-15, 17-19 and 20 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support. The Examiner acknowledges that the specification enables a method of inhibiting urogenital pathogen colonization of the urogenital tract in women by orally or vaginally administering a therapeutically effective amount of at least on *Lactobacillus iners* and a pharmaceutically acceptable carrier. However, the Examiner alleges that the specification does not provide enablement for a method of maintaining a healthy urogenital flora in females by administering *L. iners* via any route or a method for treating any infection. Further, The Examiner alleges that the specification does not provide enablement for a method of establishing a healthy bacterial flora in a female throughout life. The Examiner indicates that Applicants in the previous response referred to Anukam et al. (Anukam et al., Yogurt containing probiotic

[1] Applicants note that the Examiner does not disagree that *L. iners* is fundamentally present in the intestine and vagina. Indeed, the Examiner acknowledges that it was known that different microbes are present in humans. The present invention employs *L. iners* as a means to modulate the flora and confer health benefits. The administration of *L. iners* can act to reduce the pathogens that ascend from the intestine to the vagina, or in the vagina itself. The *L. iners* can create an environment more conducive to health. Thus, the common effect is that *L. iners* acts on both sites. There is no burden on part of the Examiner to conduct separate search as several studies, such as Morelli et al. (2004) and Antonio et al. (2005), have clearly shown the link between *lactobacilli* in the vagina and intestine.

Lactobacillus rhamnosus GR-1 and L. reuteri RC-14 helps resolve moderate diarrhea and increases CD4 count in HIV/AIDS patients. *J. Clin. Gastroenterol.* 2007; *in press*.) ("Anukam et al. 2007") but did not provide a copy of the publication. The Examiner therefore has not considered the Anukam et al. 2007 reference.

In the first instance, Applicants note that in view of the Applicants' amendments to the claims in the previous response, the Examiner has withdrawn the enablement rejection of Claims 1-7 and 13.

With respect to the Examiner's allegation that *L. iners* is only effective for human disease related to infections in the vaginal tract, Applicants argued in the previous response that orally administered probiotic *lactobacilli* have been shown to provide benefits to the respiratory and urinary tracts. Applicants argued that the present invention recognizes that *L. iners* can provide similar benefits. Particularly, Applicants indicated to the Examiner that evidence existed in support of the effectiveness of administering *L. iners* for treatment of diseases other than vaginal tract infections. Applicants referred to Anukam et al. 2007, which confirmed that probiotic *lactobacilli* could boost the CD4 count in HIV/AIDS patients. Applicants hereby submit a copy of Anukam et al. 2007 reference as **Exhibit 1**.

The Examiner alleges that the specification does not demonstrate that *L. iners* can treat or prevent <u>any</u> infection. In the first instance, Applicants respectfully submit that the law is clear that a patent application is not required to describe the information or knowledge that is well known to one skilled in the art. Applicants respectfully submit that the present invention employs *L. iners* as a means to modulate the flora and confer health benefits. As mentioned above in Footnote 1, the Examiner does not disagree that *L. iners* is fundamentally present in the intestine <u>and</u> vagina. Indeed, the Examiner acknowledges that different microbes are present in humans. Applicants respectfully submit that the administration of *L. iners* can act to reduce the

pathogens that ascend from the intestine to the vagina, or in the vagina itself. The *L. iners* can create an environment more conducive to health. Thus, *L. iners* acts on both intestinal and vaginal sites. Several studies, such as Morelli et al. (2004) (copy of the Abstract is enclosed as **Exhibit 4**) and Antonio et al. (2005) (copy of the Abstract is enclosed as **Exhibit 5**), have clearly shown the link between *lactobacilli* in the vagina and intestine. Applicants respectfully submit that the common appearance of *L. iners* in the intestine and vagina makes *L. iners* a perfect choice to one skilled in the art to apply it in both the intestine and vagina. Applicants respectfully submit that the inherent anti-infective and immune modulatory properties of *L. iners* had been well known to one skilled in the art at the time the present application was filed. Applicants also submit that it had been well known to one skilled in the art that many organisms (e.g., *streptococci*, *staphylococci*, *E. coli*, *Pseudomonas*, and *Prevotella*) that infect the intestine and vagina also infect at other sites, such as wounds and lung. As such, Applicants respectfully submit that one skilled in the art in view of the teaching of the present application together with the well-known knowledge, would not only consider *L. iners* for more widespread therapy but can also use *L. iners* for treating or preventing any infection, without undue experimentation.

For example, a recent study in Russia has shown *lactobacilli* can benefit people with cancerous lesions as well. See **Exhibit 2**. Moreover, Anukam et al. (*Microbes Infect.* 2006 May; 8(6): 1450-54) ("Anukam et al. 2006") (copy is enclosed as **Exhibit 8**), which was referred to and discussed in the previous response, illustrates that probiotic *lactobacilli* augment the efficacy of antibiotics in treating infections. Anukam et al. 2006 shows the commonality between African women and others, in that *L. iners* is the most, or one of the most, common *lactobacilli*. Applicants respectfully submit that the Examiner appears to have missed the fact that this commonality constitutes universal application of the *L. iners* to all women.

The Examiner alleges that the present application does not provide enabling disclosure with respect to applicability of *L. iners* for treating infections caused by viruses and fungi. In this regard, Applicants respectfully submit that the applicability of *lactobacilli* to viruses and fungi-caused infections was well known at the time the present application was filed. For example, *lactobacilli* are often used to treat rotavirus diarrhea. As such, Applicants respectfully submit that one skilled in the art in view of the teaching of the present application together with the well-known knowledge can apply *L. iners* to treat infections caused by viruses and fungi, without undue experimentation.

In terms of treating bacterial vaginosis by *L. iners*, Applicants refer to a recent article by Saunders et al. (*Colloids Surf. B: Biointerfaces* (2007), doi:10.1016/j.colsurfb.2006.11.040), a copy of which is enclosed as **Exhibit 3**. Saunders et al. explicitly teach the ability of *L. iners* to interfere with biofilms integral to bacterial vaginosis.

Applicants further respectfully submit that establishing a healthy bacterial flora in a female throughout life does not mean that *L. iners* administration will provide life-long benefits with one dose, but rather means that *L. iners* administration can provide benefits at any time during the life. The specification on page 8, lines 15-17 clearly teaches that by "throughout life" is meant "in the neonatal period, during childhood and in the pre-menopausal and post-menopausal periods." For example, in some cases, the *L. iners* may have to be taken regularly; in other cases the use of *L. iners* may allow the woman's own flora to recover sufficiently for her to maintain a healthy state for a long period of time. Applicants respectfully submit that it is well known to one skilled in the art that bacterial vaginosis is a condition in which *lactobacilli* are depleted and the vaginal pH is elevated above 4.5. This condition is highly prevalent and well known to physicians. Thus, any physician would know how to diagnose health and absence of bacterial vaginosis at the time the present application was filed.

Applicants respectfully submit that the method of using *lactobacilli* for treating an infection has been further supported recently in the scientific literature, in which antibiotic and anti-fungals were used in conjunction with *lactobacilli*. Indeed, a recent study has suggested that for some drugs, there is increased bioavailability when *lactobacilli* are co-added.

Moreover, the Examiner is concerned with the range of *L. iners* applications, which can be widely divergent. In this regard, Applicants respectfully submit that unlike pharmaceutical agents designed for limited application, *lactobacilli* are integral to human health and thus can affect many conditions, including cardiovascular, intestinal, respiratory, urogenital and others. The effectiveness differs with the condition. For example, the effect of *lactobacilli* for bacterial vaginosis is through displacing pathogens from the vagina (Saunders et al. 2007); the effect of *lactobacilli* for HIV/AIDS it is through boosting immunity and eradicating diarrhea (Anukam et al. 2007); and the effect of *lactobacilli* for cervical cancer is through down-regulation of inflammation, which is a factor shown by *lactobacilli* in two recent studies (Kim et al. 2006; Baroja et al. 2007) (copies are enclosed as **Exhibits 6 and 7**, respectively). The route of administration can also vary. For example, Anukam et al. 2006b show intravaginal use of *lactobacilli* was shown to cure bacterial vaginosis better than antibiotics.

The Examiner alleges that the term "treatment of an infection" as recited in Claim 19 encompasses a method of curing an infection. Applicants respectfully submit that the term "treatment" is clearly defined by the specification at the bottom of page 18 as effective inhibition and prevention of the infection. The specification defines "therapeutically effective amount" as "an amount of probiotic organism, e.g., *Lactobacillus iners*, high enough to significantly positively modify the condition to be treated but low enough to avoid serious side effects (at a reasonable benefit/risk ratio), within the scope of sound medical judgment." See bottom of page 11. The specification also provides that a therapeutically effective amount of *Lactobacillus iners*

will vary with the particular goal to be achieved, the age and physical condition of the patient being treated, the severity of the underlying disease, the duration of treatment, the nature of concurrent therapy and the specific *Lactobacillus iners* strain employed. *Id.* In addition, the specification exemplifies a therapeutically effective amount under different goals or in different conditions. See the bridging paragraph of pages 11-12. For example, the specification provides that "*Lactobacillus iners* administered to a child or a neonate will be reduced proportionately in accordance with sound medical judgment. The effective amount of *Lactobacillus iners* will thus be the minimum amount which will provide the desired attachment to epithelial cells. For example, the presence of 5×10^9 bacteria . . . is effective when administered in quantities of from about 0.05 ml to about 20 ml." *Id.* As such, Applicants respectfully submit that for treatment of an infection, a therapeutic amount does not mean the amount that can "cure" all infection. One skilled in the art in view of the present application and well known knowledge in the art can determine the appropriate therapeutic amount, which may vary from person to person. For example, in vaginal treatment the appropriate therapeutic amount may be 1000 to 10 billion bacteria, while in the oral application the appropriate therapeutic amount may be 1 million to 50 billion.

Therefore, Applicants respectfully submit that in view of the present application and well known knowledge in the art, one skilled in the art can make and use the appropriate *lactobacilli* in the methods as claimed in the present application, without undue experimentation. In view of the foregoing argument and the amendment to the claims, the rejection of Claims 14-15, 17-19 and 20 under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support, is overcome and withdrawal thereof is respectfully requested.

The Examiner maintains the rejection of Claim 15 under 35 U.S.C. §102(e) as allegedly anticipated by Falsen et al. *(Journal of Systematic Bacteriology* 217-221, 1999).[2] According to the Examiner, a prebiotic broadly encompasses any growth media that enhances the growth of the bacteria (e.g., serum added to the media). Therefore, the Examiner concludes that the Falsen et al. anticipate the present invention by teaching a new isolated species of *Lactobacillus: L. inners* that grows in an agar culture supplemented with 5% horse blood at 37°C in air plus CO_2, which is further prepared in SDS (Sodium Dodecyl Sulfate) for protein quantification.

Applicants observe that, as acknowledged by the Examiner, Falsen et al. simply identify a *L. iners* organism, which identification by itself, without more, does not teach or suggest that the *L. iners* organism can be placed in a pharmaceutical or food carrier and delivered for therapeutic purposes. In this regard, Applicants respectfully submit that there are many bacteria types discovered each month, some through growth on blood agar as described in Falsen et al. However, Applicants respectfully submit that the fact that bacteria are kept live on blood agar does not teach or suggest that blood agar can be a prebiotic or good delivery vehicle for humans. Nowhere does the cited reference teach or suggest that the agar mentioned in the reference as either a prebiotic or a pharmaceutical carrier. Indeed, Applicants respectfully submit that blood agar is not a prebiotic, because its contents can be digested in the body and do not require *lactobacilli*. In fact, many organisms, including pathogens, can digest this agar and serum, making these very bad choices for a carrier. As such, one skilled in the art in view of the present application will recognize that blood agar and serum are not prebiotics or suitable carrier vehicles for *lactobacilli* application to health.

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[2] Since the cited reference is neither a published patent nor a published patent application, the rejection should have been raised under 35 U.S.C. §102(b).

As such, Applicants respectfully submit that the Falsen et al. reference does not teach or suggest a pharmaceutical composition comprising *L. iners*, a prebiotic and a pharmaceutically acceptable carrier. Therefore, the rejection of Claim 15 under 35 U.S.C. §102(b) as allegedly anticipated by Falsen et al. is overcome and withdrawn thereof is respectfully requested.

Claims 3 and 20 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The Examiner contends that Claim 3 is vague and indefinite by referring *L. iners* to the number "Y16329." The Examiner states that Claim 20 recite the phrase "displacing vaginal pathogens". The Examiner contends that the specification discloses at page 7, last paragraph that "the *Lactobacillus iners* of the present invention will inhibit growth and/or adhesion of enteric pathogens to gastrointestinal surfaces". Thus, the Examiner alleges that it is unclear whether "displacing vaginal pathogens" refers to inhibiting binding other vaginal pathogen or competing with pathogens already bound to the vaginal mucosa to release them.

In an effort to favorably advance prosecution, Applicants have canceled Claim 3, without prejudice. Applicants reserve the right to pursue the subject matter of Claim 3. With respect to the phrase "displacing vaginal pathogens" recited by Claim 20, Applicants respectfully submit that in order for pathogens to be displaced, in most instances it is because their growth or adhesion has been interfered with, and the environment has no longer become conducive to them staying in that condition. In addition, the Saunders et al. 2007 reference confirms that one skilled in the art would understand the meaning of the term "displacement" or the phrase "displacing vaginal pathogens."

Therefore, Applicants respectfully submit that the rejection of Claim 20 under 35 U.S.C. §112, second paragraph, is overcome and the rejection of Claim 3 under 35 U.S.C. §112, second paragraph, is moot in view of the cancellation of Claim 3. Withdrawal of the rejection of Claims 3 and 20 under 35 U.S.C. §112, second paragraph, is respectfully requested.

Claim 20 is rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleges that the subject matter "displacing vaginal pathogens" as recited in Claim 20 is not described in the specification.

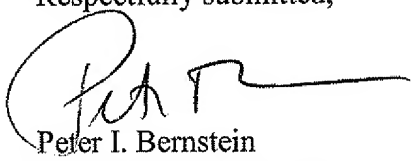
Applicants observe that as acknowledged by the Examiner, the specification teaches that "[t]he *Lactobacillus iners* of the present invention will inhibit growth and/or adhesion of enteric pathogens to gastrointestinal surfaces including those that cause enteric infections." See the last paragraph of page 7 of the specification (emphasis added). "The introduction or administration of *lactobacilli* probiotics to the intestine and passage onto the urogenital tract . . . modulates the immune response against infection and disease and reduces the risk of medical device associated infections . . . Accordingly . . . host responses are stimulated which inhibit pathogens and/or create a microenvironment less conducive to pathogen spread in women" and "a combination of adhesion of *Lactobacillus iners* and the production by *Lactobacillus iners* of one or more inhibitory substances is responsible for excluding pathogens and/or reducing their numbers at the site of a gastrointestinal or genito-urinary infection." See paragraphs 2-3 on page 13 of the specification (emphasis added).

Applicants respectfully submit that the language "displacing vaginal pathogens" concerns at least inhibitor displacement and exclusion. Based on the teaching of the present application, it would be clear to one skilled in the art that Applicants were in possession of the subject matter "displaced vaginal pathogens," either by inhibiting growth or adhesion of the pathogen or excluding the pathogen. See also Saunders et al. *Coll. Surf. B: Biointerfaces* 2007: 55: 138-142 and **Exhibits A, B and C** submitted in the previous response.

As such, the rejection of Claim 20 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement is overcome and withdrawal thereof is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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